tolbutamide applies to all other sulfonylurea drugs as well. Therefore, the labeling for oral hypoglycemic drugs of the sulfonylurea class shall include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraph (b) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea class shall include in boldface type at the beginning of the ''Warnings'' section of the labeling the following statement:

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes,* 19 (supp. 2): 747–830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of (name of drug) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

[49 FR 14331, Apr. 11, 1984]

§ 310.519 Drug products marketed as over-the-counter (OTC) daytime sedatives.

(a) Antihistamines, bromides, and scopolamine compounds, either singly or in combinations, have been marketed as ingredients in over-the-counter (OTC) drug products for use as daytime sedatives. The following claims have been made for daytime sedative products: ''occasional simple nervous tension,'' ''nervous irritability,'' ''nervous tension headache,'' ''simple nervousness due to common every day overwork and fatigue,'' ''a relaxed feeling,'' ''calming down and relaxing,'' ''gently soothe away the tension,'' ''calmative,'' ''resolving that irritability that ruins your day,'' ''helps you relax,'' ''restlessness,'' ''when you're under occasional stress . . . helps you work relaxed.'' Based on evidence presently available, there are no ingredients that can be generally recognized as safe and effective for use as OTC daytime sedatives.

(b) Any OTC drug product that is labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any OTC daytime sedative drug product introduced into interstate commerce after December 24, 1979, that is not in compliance with this section is subject to regulatory action.

[44 FR 36380, June 22, 1979; 45 FR 47422, July 15, 1980, as amended at 55 FR 11579, Mar. 29, 1990]

§ 310.525 Sweet spirits of nitre drug products.

(a) Historically, sweet spirits of nitre has been present as an ingredient in over-the-counter (OTC) drug products for various uses. Based upon the lack of adequate data to establish effectiveness for any use and the adverse benefit-to-risk ratio, sweet spirits of nitre

drug products cannot be considered generally recognized as safe and effective. The benefit from using sweet spirits of nitre for any use is insignificant when compared to the risk.

(b) Any drug product containing sweet spirits of nitre is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any drug product containing sweet spirits of nitre for any use is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any drug product containing sweet spirits of nitre in interstate commerce after June 27, 1980, that is not in compliance with this section is subject to regulatory action.

[45 FR 43401, June 27, 1980, as amended at 55 FR 11579, Mar. 29, 1990]

§ 310.526 Camphorated oil drug products.

(a) Historically, camphorated oil (also known as camphor liniment), a solution of 20 percent camphor in cottonseed oil, has been marketed as an over-the-counter (OTC) drug product for various uses, primarily as a topical counterirritant or liniment. A large number of accidental ingestions of camphorated oil, often mistaken for castor oil, cod liver oil, mineral oil, olive oil, cough medicine, or other drug products, have been reported and toxicity has often resulted, primarily in infants and young children. Because of the potential hazard for poisoning to occur, the benefit from using any drug product containing camphor in oil or from using any camphor-containing drug product that is labeled as ''camphorated oil'' or ''camphor liniment,'' or any similar name such as ''camphor oil'' or ''camphorated liniment,'' for any use, is insignificant when compared to the risk. Based upon the adverse benefit-to-risk ratio, camphorated oil, any drug product containing camphor in oil, or any other drug product containing camphor that is represented, suggested, or purported to be camphorated oil, such as a product labeled ''camphor liniment,'' ''camphor oil,'' ''camphorated liniment,'' or any similar name, cannot be considered generally recognized as safe.

(b) Any camphorated oil drug product, any drug product containing camphor in oil, or any other drug product containing camphor that is represented, suggested or purported to be camphorated oil, e.g., ''camphor liniment,'' ''camphor oil,'' ''camphorated liniment,'' is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any camphorated oil drug product, any drug product containing camphor in oil, or any other drug product containing camphor that is represented, suggested, or purported to be camphorated oil, e.g., ''camphor liniment,'' ''camphor oil,'' ''camphorated liniment,'' is safe for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any such drug product in interstate commerce after September 21, 1982 that is not in compliance with this section is subject to regulatory action.

[47 FR 41720, Sept. 21, 1982, as amended at 55 FR 11579, Mar. 29, 1990]

§ 310.527 Drug products containing active ingredients offered over-the-counter (OTC) for external use as hair growers or for hair loss prevention.

(a) Amino acids, aminobenzoic acid, ascorbic acid, benzoic acid, biotin and all other B-vitamins, dexpanthenol, estradiol and other topical hormones, jojoba oil, lanolin, nucleic acids, polysorbate 20, polysorbate 60, sulfanilamide, sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons, tetracaine hydrochloride, urea, and wheat germ oil have been marketed as ingredients in OTC drug products for